# Use of Oral Isotretinoin in the Management of Rosacea

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## Abstract

Rosacea is a chronic inflammatory disease affecting roughly 16 million Americans. Topical and oral antibiotic/anti-inflammatory agents are currently the mainstay of therapy and are often used in combination. In this article, the authors discuss the use of oral isotretinoin in the management of rosacea, exploring dosage, comparable efficacy, safety, and cost.

## Introduction

Isotretinoin (13-cis-retinoic acid) is a synthetic retinoid derived from retinol (vitamin A) that is primarily used orally for the treatment of refractory nodulocystic acne vulgaris and is approved by the United States Food and Drug Administration (FDA) for this indication.[1] As far back as 1981, around the time oral isotretinoin was being prepared for release to the marketplace in the United States for acne treatment, efficacy in rosacea was already observed.[2] In addition to its ability to decrease the size of sebaceous glands and reduce sebum production, *in-vivo* testing demonstrated that oral isotretinoin exhibits certain anti-inflammatory properties, and thus may be effective in a variety of inflammatory dermatoses.[3] Isotretinoin also exhibits immunomodulatory properties that may be synergistic with those of interleukin (IL)-2 or interferon (IFN)-α and has been found to be effective in combination treatment for disorders, such as condyloma acuminata.[4–6] Another important observation with isotretinoin is its antineoplastic activity, especially with squamous cell epithelial neoplasms, which has been substantiated by its ability to reduce tumors and decrease the development of nonmelanoma skin cancer, especially in immunosuppressed patients (i.e., organ transplant recipients).[7–10] Over time, oral acitretin, another oral retinoid, has replaced oral isotretinoin for this latter application.

Rosacea is a common inflammatory dermatosis, most commonly affecting the face of adults, that is associated with characteristic visible signs and symptoms.[11] However, signs and symptoms of rosacea can exhibit interpatient variability in presence and severity as well as variability with the clinical subtype. The major clinical subtypes of rosacea were collectively defined in the literature by a consensus group less than one decade ago, allowing clinicians to better differentiate the clinical subtypes of rosacea and correlate these defined diagnostic subtypes with the treatment options most likely to be effective in each case.[11] The four major clinical subtypes of rosacea are erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea, and ocular rosacea. Although these subtypes of rosacea do not represent progressive stages of disease, a given patient may present with or develop more than one subtype of rosacea. Importantly, the presence and severity of ocular rosacea do not correlate with the severity of cutaneous involvement with rosacea, and flares of these subtypes in a given patient affected by both are not necessarily concurrent.

A variety of topical agents, oral agents, and physical modalities are available to treat specific clinical findings seen in different subtypes of rosacea. Specific therapies are of benefit for findings associated with some subtypes, but not necessarily others.[12] The majority of clinical studies evaluating the major medical therapies used for rosacea have assessed efficacy and safety in patients with PPR, with some smaller studies and case reports evaluating phymatous rosacea and ocular rosacea.[12] Physical modalities are

typically used to treat "fixed" vascular changes, such as telangiectasias and persistent diffuse erythema.

Three topical medications approved by the FDA for PPR are metronidazole 0.75% and 1% formulations and azelaic acid gel 15%. Other topical treatments used "off label" based on a limited number of small studies and case reports are benzoyl peroxide-clindamycin, erythromycin and clindamycin, tacrolimus, pimecrolimus, and tretinoin.[12]

Topical sulfacetamide-sulfur "leave-on" and wash formulations, although not formally approved by the FDA for any indication based on pivotal studies, is supported for treatment of seborrheic dermatitis, acne vulgaris, and rosacea based on an official monograph with "grandparented" approval.[12] Oral antibiotics, including tetracycline (TCN) agents, are not approved by the FDA for treatment of any subtype of rosacea, although there is widespread experience with TCN agents for more than four decades, primarily for PPR.[12] However, a modified-release 40mg capsule formulation of doxycycline administered once a day is FDA approved for PPR, with data supporting efficacy, safety, and absence of antibiotic activity (subantimicrobal dosing).

Oral metronidazole has been reported as another oral alternative for the treatment of rosacea and has been utilized most often by European practitioners.[12–15]

## What data are available on the use of oral isotretinoin for dermatological disorders other than the major facial inflammatory dermatoses acne vulgaris and rosacea?

**Psoriasis.** Three major pathogenic features of psoriasis are addressed therapeutically by retinoids including disturbed keratinocyte differentiation, keratinocyte hyperproliferation, and inflammatory cell infiltration.[4,16] Although oral isotretinoin is not a commonly discussed alternative for treatment of psoriasis, some studies have shown beneficial effects in patients with psoriasis, primarily the pustular type.[4,17–20] The combination of oral isotretinoin and psoralen plus ultraviolet A light (PUVA) has also been reported to be beneficial in patients with psoriasis.[17,20]

**Pityriasis rubra pilaris.** Oral isotretinoin has been used for the treatment of pityriasis rubra pilaris (PRP), with reports ranging in "N size" from 4 to 45 patients, with treatment durations ranging between 16 to 24 weeks.[21–24] Reported therapeutic benefits, such as 50-percent improvement within 16 weeks or complete or near complete clearance of PRP within six months of therapy, have been described in the literature.[21–24] The dosage of oral isotretinoin dosage used in these reports ranged from 0.5 to 2mg/kg/day.[21–24]

**Condylomata acuminata.** Variable success has been noted with use of oral isotretinoin for the treatment of condylomata acuminata (CA). Among 56 patients with CA treated with oral isotretinoin 1mg/kg/day for three months, 25 (47.1%) exhibited no response, 7 (13.2%) demonstrated a partial response, and 21 (39.6%) responded completely.[25] Recurrences at 38 weeks and 46 weeks were noted among two of the 21 patients who had demonstrated a complete response initially.

Another report documented no response in seven patients with CA treated with oral isotretinoin monotherapy.[26] On the other hand, of 42 male patients with CA treated with oral isotretinoin, 26 patients were completely free of lesions and without recurrence during a mean follow-up period of 10.14 months.[4,5] The remaining 16 patients showed reductions in the size and number of CA lesions. In the same study, 40 of 44 patients treated with both interferon α-2a (IFNα-2a) and oral isotretinoin were completely free of lesions and without recurrence over a mean follow-up period of 17.9 months.[4,5] An additional study demonstrated an 84.8-percent remission rate in females treated with this same combination therapy compared to 75-percent achieved with oral isotretinoin monotherapy.[6] These data support that the combination of oral isotretinoin and IFNα-2a is more effective than oral isotretinoin monotherapy.

**Basal cell carcinoma.** Oral isotretinoin 0.4mg/kg/day has been shown to be effective in preventing the development of basal cell carcinomas (BCCs) in patients with nevoid basal cell carcinoma (NBCC) syndrome.[27] However, in patients with BCC who do not have this syndrome, results have not been as promising. In a small case series where 12 patients were treated with a mean daily dose of oral isotretinoin 3.1mg/kg/day, only 22 of 270 tumors (8.1%) underwent complete regression.[28] In another study, oral isotretinoin 10mg/day administered for 36 months in patients with BCC demonstrated poor efficacy in reducing the development of new BCCs and a significant risk of adverse systemic effects.[29]

**Disseminated superficial actinic porokeratosis.** The combinations of low-dose oral isotretinoin and topical fluorouracil or topical calcitriol, have been reported to be effective in the treatment of

disseminated superficial actinic porokeratosis and actinic keratosis, respectively.[30–32]

**Squamous cell carcinoma.** Oral isotretinoin combined with subcutaneous IFNα-2a displayed a treatment success rate in more than 60 percent of patients with nonpenile squamous cell carcinoma (SCC).[33–35] However, no satisfactory therapeutic results have been obtained with oral isotretinoin monotherapy in patients with advanced SCC.[1,4,33–36]

**Melanoma.** Oral retinoids have not been found to be beneficial for the treatment of dysplastic nevi and melanomas.[4,37–39] However, metastatic malignant melanoma was treated in 25 patients with the combination of oral isotretinoin 1mg/kg/day and subcutaneous recombinant IFNα-2a, administered for 16 to 48 weeks, with 20 percent demonstrating a complete or partial response.[40] Most of the patients demonstrating response had limited tumor burden with disease confined to the skin and lymph nodes.[4,40]

**Lymphoma.** Oral isotretinoin has been used in combination with PUVA or IFN in patients with lymphomas. A synergistic effect appeared to occur with symptomatic relief provided.[41–44] In one trial, a complete or partial remission was noted in 82 percent of patients.[45]

**Other skin diseases.** Oral isotretinoin has been employed in other non-acne skin diseases, with positive results noted in some cases. These conditions include granuloma annulare, particularly the disseminated form, cutaneous lupus erythematosus, confluent and reticulated papillomatosis, and lamellar ichthyosis.[46–50] It also has been used to help prevent future internal malignancies in Muir-Torre syndrome patients either alone or in combination with IFNα-2a.[51,52]

## What data is available on the use of oral isotretinoin for rosacea?

Multiple reports from the 1980s established the effectiveness of oral isotretinoin for rosacea.[12,15,53–57] Importantly, recalcitrant cases of rosacea have been successfully treated with oral isotretinoin using a dosage range of 0.5 to 1mg/kg/day.[58,59] In a multicenter study (N=92) with severe PPR, treatment with a 20-week course of oral isotretinoin was described as very effective.[60] With regard to a possible therapeutic mechanism, a study group on oral isotretinoin showed significantly reduced facial cutaneous blood flow by means of laser-Doppler at both 25 and 34°C at 10 weeks.[61] In a study of refractory PPR (N=22), oral isotretinoin 10mg daily over a maximum duration of four months significantly reduced inflammatory lesions (papules, pustules) and erythema at nine weeks, with further improvement at 16 weeks.[62]

A young female patient with perioral granulomatous rosacea was successfully treated with a 20-week course of oral isotretinoin with clearance of the eruption.[7] Oral isotretinoin has also been shown to decrease nasal volume in rhinophyma that is sebaceous in type in the prefibrotic stage.[12,53,61,63,64] This success is likely related to the ability of oral isotretinoin to markedly reduce sebaceous gland size.[1]

## Are data available suggesting that oral isotretinoin may serve as an alternative to oral antibiotics for the treatment of rosacea?

Gollnick et al[65] conducted a large-scale, placebo-controlled, randomized, 12-week, multicenter study with head-to-head comparison of oral isotreinoin versus doxycycline for PPR or phymatous rosacea (N=573). Patients with rosacea subtype II (papulopustular) or subtype III (phymatous) with eight or more inflammatory lesions at baseline, a global physician assessment score of at least moderate severity, and the presence of the disease for at least three months were included in the study. Enrolled subjects received one of three different daily dosage regimens with oral isotretinoin: 0.1mgkg, 0.3mg/kg, or 0.5mg/kg, doxycycline 100mg daily for 14 days then 50mg daily, or placebo. All three isotretinoin doses produced a greater reduction in inflammatory papules, pustules, and nodules as compared to the placebo group. Only the oral isotretinoin dosage of 0.3mg/kg demonstrated a statistically significant superiority over placebo ($p$=0.00523). Doxycycline also proved to be statistically superior to placebo ($p$=0.00501). Oral isotretinoin 0.3mg/kg/day was compared to doxycycline in a second study phase that demonstrated noninferiority of this oral isotretinoin daily dosage (0.3mg/kg) to doxycycline ($p$=0.00001). At the end of the study, 24 percent of patients treated with oral isotretinoin 0.3mg/kg/day achieved remission in comparison to 13.6 percent in doxycycline-treated patients. Patient ratings of treatment results at the end of therapy were more frequently rated as "excellent improvement" (32.6%) as compared to 24 percent in those treated with doxycycline. Based on the results of this study, it appears that oral isotretinoin 0.3mg/kg/day is an efficacious and well-tolerated option for the treatment of PPR and phymatous rosacea and may be used successfully as an alternative to oral antibiotics in selected cases.

### Are there any data available on the use of continuous "microdose" isotretinoin in recalcitrant rosacea to avoid recurrence when isotretinoin is discontinued?

Continuous "microdose" isotretinoin (CMI) treatment (0.04–0.11mg/kg/day) has been shown to be sufficient to control persistent adult acne vulgaris.[14] Hofer[66] looked at two groups of 12 patients with recalcitrant rosacea. Group 1 had recalcitrant rosacea previously treated with topical metronidazole and several cycles of oral antibiotics. Patients in this group initially received oral isotretinoin, 10 or 20mg daily, over a period of 4 or 6 months. Oral isotretinoin was then reduced to an individual continuous minimal dose, which ranged from 0.03 to 0.17mg/kg/day (mean, 0.07mg/kg/day). Group 2 had different grades of untreated rosacea. The Dermatology Life Quality Index (DLQI) was used to measure the degree of disability caused by rosacea, covering symptoms and feelings, daily activities, leisure activities, personal relationships, and treatment. The resultant DLQI can range from 0 to 30. The mean DLQI score in Group 1 was 1.16 in comparison to a mean score of 8.1 in the untreated Group 2. The efficacy of CMI was well demonstrated by the low mean post-treatment DLQI score in Group 1 ($P$=0.0001). While long-term use of oral isotretinoin with cumulative doses of up to 1,075mg/kg did not cause any significant radiological abnormalities, cumulative doses per year of 11 to 62mg/kg (mean, 24.4mg/kg) in Group 1 patients, which included three patients on CMI for longer than 30 months, fell well below this total dosage value.[66] Hofer suggests that CMI can be considered as an alternative to repeat courses of systemic antibiotics in the treatment of recalcitrant rosacea in adult patients as long as appropriate precautions and monitoring are carried out. CMI may also be considered in patients who prefer to avoid relapse upon discontinuation of oral isotretinoin. If CMI is utilized, it is crucial that clinicians employ a rational approach to long-term monitoring and establish proper contraception in premenopausal female patients of childbearing potential due to the risk of teratogenicity. Importantly, all patients treated with oral isotretinoin in the United States must be enrolled in and follow the requirements of the iPledge program.

### What treatment regimen has been recommended for rosacea fulminans (pyoderma faciale) with oral isotretinoin?

Oral isotretinoin in combination with systemic corticosteroids has been used successfully to treat cases of rosacea fulminans.[67,68] Rosacea fulminans, also referred to as pyoderma faciale, is a rare disease, usually affecting female patients with an age distribution from the teens to the 40s. A case of a three-year-old girl diagnosed with rosacea fulminans presented with several facial erythematous papules, pustules, inflammatory nodules, and purulent sinus tracts present for three months.[67] Prior treatments with topical and systemic antimicrobials as well as topical corticosteroids had no effect. The infant was then treated with oral erythromycin 250mg four times daily, oral prednisolone 0.5mg/kg/day with tapering over two weeks, fluocinolone acetonide 0.025% cream, and warm compresses for two weeks with moderate improvement. At this point, oral isotretinoin 10mg (0.75mg/kg) daily was introduced. There was marked improvement after four weeks, with complete clearance by eight weeks. Oral isotretinoin was very well tolerated for a total of 24 weeks without significant adverse effects. One year after completion of treatment, no relapse was noted.

A short course of systemic corticosteroids in combination with oral isotretinoin is often effective therapy for rosacea fulminans. Oral prednisolone may be started initially at 1mg/kg/day for 1 to 2 weeks with a slow tapering of the daily dose over the next 2 to 3 weeks. Oral isotretinoin may be started at 0.2 to 0.5mg/kg/day for 3 to 4 months, with a dose of 0.3mg/kg/day suggested by the authors. Other authors have suggested use of oral isotretinoin at a daily dosage of at least 1mg/kg.[69–71]

### Are there data on the use of oral isotretinoin in patients with concomitant inflammatory bowel disease?

A 28-year-old woman with underlying ulcerative colitis was treated with oral isotretinoin despite concern regarding an alleged association between use of oral isotretinoin and development or exacerbation of inflammatory bowel disease (IBD).[68] Oral isotretinoin at 1mg/kg/day was instituted and used over a duration of 20 weeks. Although most of the affected areas resolved completely within 20 weeks, the oral isotretinoin dose was continued at 0.5mg/kg/day for an additional 12 weeks in an attempt to clear residual papulonodular lesions that were still present on some areas on the face. After a total of 32 weeks on oral isotretinoin, complete resolution was achieved and the patient remained clear over one year of follow up. Controversy still exists regarding an association between oral isotretinoin use and IBD; however, a definitive association has not been established.

If in fact oral isotretinoin causes or exacerbates IBD, the association is idiosyncratic and rare.

### What information is available comparing the costs of various rosacea treatments, including oral isotretinoin?

Untreated or under-treated rosacea can have a significant impact on quality of life and possibly lead to permanent disfigurement depending on severity and subtype.[72–74] Thomas et al[72] estimated average daily costs (ADC) based on treatment frequency and estimated gram usage for topical application of metronidazole gel (0.75% and 1%), azelaic acid (15% gel or 20% cream), sodium sulfacetamide and sulfur 10%/5% lotion, and oral regimens including tetracycline 250mg/day, doxycycline-modified release 40mg capsules administered at one capsule (40mg) daily, and oral isotretinoin 40mg/day. The ADC was divided based on efficacy rates derived from clinical trials to calculate costs per success. Costs per success were then combined with office visit costs to estimate the total cost for each treatment over a 15-week period. The ADC for oral isotretinoin for rosacea was markedly higher than other therapies, with the 15-week total cost estimated to be approximately $2,500.00. As Thomas et al[72] discussed in their review, estimating the cost of treatment on a "per-success" basis was difficult for various reasons. They reported a paucity of head-to-head trials that directly compare the different treatments. Data for oral isotretinoin were only available in a head-to-head trial comparing it to topical tretinoin.[75] In this specific study, 22 patients with severe or recalcitrant rosacea were divided into groups in a randomized, double-blind trial that compared low-dose oral isotretinoin 10mg/day, topical tretinoin 0.025% cream once daily, and the combined use of both oral isotretinoin and topical tretinoin. Treatment with oral isotretinoin appeared to give a more rapid onset of improvement, no differences between groups was noted after 16 weeks of treatment, and no additive benefit was observed with the combined use of oral isotretinoin and topical tretinoin. Another limitation noted by Thomas et al discussed was the lack of a standardized methodology for judging success in clinical trials of rosacea, including specific subtypes.[72] Most trials evaluate the quantifiable measure of reduction in inflammatory lesions, often without data on reduction in erythema and telangiectasia. Due to the variability of specific rosacea subtypes and the marked clinical differences between the visible signs of the disease (i.e., inflammatory lesions, perilesional erythema, vascular or neurogenic erythema, telangiectasias) and their response to treatment, meaningful interpretation of "treatment success" noted in different reports remains an unresolved challenge.

Additionally, rosacea treatment may often be used in combination for patients who present with different clinical subtypes. Combination therapies may include use of both topical and oral medications for moderate-to-severe PPR or a combination of topical and/or oral medical therapies with physical modalities, the former to reduce inflammatory lesions and perilesional erythema and the latter directed at clearance of telangiectasias and diffuse persistent macular erythema (vascular or neurogenic in origin). Investigations into costs of various combination therapy approaches and their actual clinical efficacy is confounded by multiple variables and lack of hard efficacy data with the many potential combination approaches.

### Has oral isotretinoin treatment been attempted in extrafacial rosacea and for what duration?

Extrafacial cutaneous rosacea (extrafacial rosacea) has been described in the literature and has been reported to occur predominantly in men, usually affecting sun-exposed skin. Extrafacial rosacea has been reported very rarely and is difficult to diagnose due to its atypical pattern and low index of suspicion.[76–79] Bostanci et al[76] described a case series of eight men diagnosed with extrafacial rosacea treated with oral isotretinoin 10mg/day for patients under 85kg and 20mg/day for patients over 85kg.[76] All eight patients completed at least two months of therapy for up to 10 months duration. The clinical response to oral isotretinoin therapy was rated as either marked improvement or complete clearance of lesions, with improvement noted after 4 to 8 weeks of therapy. Six patients were available for longer term follow up after completion of treatment, with relapse-free periods ranging from 6 to 15 months. Dry lips and facial xerosis were the reported side effects, and abnormal laboratory studies occurred, including clinically relevant changes in lipid profile.

### What final comments can be made regarding the use of oral isotretinoin for rosacea?

Available data suggests that oral isotretinoin may be used in selected cases of recalcitrant PPR, with a suggested daily dose of 0.3mg/kg. The duration of therapy to achieve complete clearance or marked improvement is variable, but often requires 3 to 4 months or greater. Ultimately, adjustment of the duration

of therapy is based on the time course of response in each patient. Dosage adjustment may be warranted but clinicians need to allow for reasonable response time, which can take several weeks to note a visible change. The disorder often recurs after cessation of oral isotretinoin therapy. Continuous microdose isotretinoin may be applicable in selected cases to control flares. Appropriate monitoring for patients on oral isotretinoin is indicated in accordance with recognized guidelines, iPledge program requirements, and specific consideration if oral isotretinoin is prescribed chronically. Appropriate contraception is warranted to prevent pregnancy in female patients of childbearing potential due to the high potential for teratogenicity with major adverse sequelae. For rosacea fulminans, oral isotretinoin (<0.5mg/kg/day for 3 to 4 months) combined with a short course of oral corticosteroid (prednisone 1mg/kg/day for 1 to 2 weeks then tapered over 2 to 3 weeks) is usually very effective.

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